REMARKS/ARGUMENTS

These Remarks are responsive to the Office Action mailed May 31, 2006 ("Office Action"). Claims 5-6, 9-14, 16-18, 35-36, 39, and 42-43 are pending in the application. Claims 9 and 39 have been amended in order to expedite allowance of this application. Applicant will pursue subject matter of the unamended claims in a divisional application. Support for the claims subject matter may be found in the original filed dependent claims and throughout the originally filed specification. Applicant respectfully requests reconsideration of the rejection of the pending claims for the following reasons.

Written Description -- 35 U.S.C. § 112, first paragraph

The Office Action rejects claims 5-6, 9-14, 16-18, 29-31, 35-36, 39, and 42-43 under 35 U.S.C. § 112, first paragraph, for lack of written description.

The Office Action recognizes that the examples in the specification involve the use of bovine chymosin. Office Action, pages 4, 5, 9, and 10. Furthermore, the Examiner "does not dispute the specification's disclosure of working examples of media comprising bovine chymosin." Office Action, page 10. The rejection of the claims for lack of written description appears to be premised upon the fact that the claims were not limited to bovine chymosin activity. For example, the Examiner stated that "[o]ther than this single species, the specification fails to disclose other representative species of the genus of recited chymosins and genes encoding therefore." Office Action, page 4. The pending claims are now limited to the use of an "organism [that] comprises a gene for encoding chymosin that is derived from a bovine or *Camelidae* species." The specification includes specific examples utilizing recombinant organisms comprising genes for encoding chymosin that is derived from a bovine species. The specification also references camel chymosin, which has been made recombinantly. *See, for example*, example 2 of WO 2001/58924, published August 16, 2001; example 1 of WO2002/36752, published May 10, 2002, which is assigned to Chr. Hansen and was filed in the United States claiming priority from November 6, 2000. Thus, Applicant has shown that the written description requirement is satisfied for the currently claimed species and the alleged failure to disclose other representative species has no bearing on the patentability of the pending

claims. Accordingly, the rejection of claims 5-6, 9-14, 16-18, 29-31, 35-36, 39, and 42-43 under 35 U.S.C. § 112, first paragraph, for lack of written description must be withdrawn.

Enablement -- 35 U.S.C. § 112, first paragraph

The Office Action rejects claims 5-6, 9-14, 16-18, 29-31, 35-36, 39, and 42-43 under 35 U.S.C. § 112, first paragraph, for lack of enablement. Applicant submits that the claim amendments to claims 9 and 34 render this ground of rejection moot for the same reasons that they render the rejection for lack of written description moot. Accordingly, the rejection of claims 5-6, 9-14, 16-18, 29-31, 35-36, 39, and 42-43 under 35 U.S.C. § 112, first paragraph, for lack of enablement must be withdrawn.

Obviousness -- 35 U.S.C. § 103

The Office Action rejects claims 5-6, 9, 12-14, 16-18, 29-31, and 42-43 under 35 U.S.C. § 103 as being unpatentable over Ward in view of Larsen.

"To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." Manual of Patent Examining Procedure § 2143.03 (8th ed., rev. 2, May 2004) (hereinafter "M.P.E.P."). "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." M.P.E.P. § 2112 (quoting Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original)). "The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." Id. (citing In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993), which reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art).

Both Ward and Larsen are discussed in the specification. Ward is discussed at page 2, lines 19-23. Larsen is discussed at page 3, lines 19-21.

Ward teaches improved production of chymosin in *Aspergillus* by expression of a glucoamylase-chymosin fusion protein. See Ward, Title & Abstract. In particular, Ward teaches that the glucoamylase-chymosin fusion proteins can be secreted at higher efficiency compared to prochymosin. Ward, page 438, col. 1, last paragraph. Ward teaches that lowering the pH to 2 converts the fusion protein to chymosin and at least some pseudochymosin. Ward, page 439, col. 2, first paragraph. Ward teaches that "[p]resumably, this would eventually be further processed to mature chymosin under appropriate conditions." Ward, page 439, col. 2, first paragraph. Ward further teaches that "[p]seudochymosin is fairly stable at a pH below 3 or above 6 but is further processed to mature chymosin at pH 4.5." Ward, page 435, col. 1, first paragraph after the Abstract. Thus, Ward suggests raising the pH to 4.5 after activating the chymosin at a pH of 2.0 to convert any pseudochymosin to chymosin.

With respect to claim 1, the Office Action mailed September 12, 2005 at page 18 correctly acknowledges that Ward does not teach "practicing their method at a pH below 2.0." Ward discloses that the inactive prochymosin can be processed at pH 2 to form pseudochymosin, which is further processed at pH 4.5 to obtain mature chymosin (Ward, col. 1) and he suggests that chymosin-glucoamylase hybrid protein might by processed the same way. Nothing in Ward teaches or suggests lowering the pH level below 2.0 as required by the claims.

Larsen discloses a method for purifying chymosin in its active form from an extract of animal stomach tissue, in which method the enzyme is claimed to be activated at a pH in the range of 0.5 to 5.0 for a period of time in the range of 10 to 120 minutes. Larson shows the optimum pH for adsorption of chymosin to the ion exchange matrix is about 2.0. See Larson, page 60, Table 11.1. Larson further teaches that the unwanted intermediate pseudochymosin is stable at low pH, but is processed to chymosin at higher pH, see Larson, page 2, line 19, which suggests raising the pH (conversion of prechymosin to pseudochymosin) in order to reduce costs.

The teachings of Ward and Larson suggest that the pH of 2.0 is the optimal pH value for the combined activation and purification of chymosin, and there is therefore no motivation to use a pH of 2.0 as it will result in lower recovery and be more expensive. The Examiner is directed to M.P.E.P. § 2145.X.D.1-3, which discusses how proceeding against common wisdom is

evidence of nonobviousness. Larsen is directed to purifying chymosin extracted from animal stomach tissue, while the claims now require the cultivation of an organism that is selected from the group consisting of a bacterial species, a yeast species and a species of filamentous fungi. Finally, there is no discussion in Larsen of glucoamylase activity, let alone "reducing the glucoamylase activity in a milk clotting composition" as claimed.

The Examiner has requested "objective evidence supporting a conclusion that activation of chymosin is optimal at pH 2.0." Office Action, page 12. Interestingly, the Examiner in the same paragraph cites Foltman which states that he has "obtained the highest yield of chymosin by a rapid activation at pH 2." Applicant further cites Kühnel et al., "Precise and efficient cleavage of recombinant fusion proteins using mammalian aspartic proteases," Protein Engineering, Vol. 6, No. 10, pp. 777-783 (2003) ("Kühnel"). Kühnel states at page 781, second column, that the "optimum pH for autocatalytic maturation of chymosin is 2." Kühnel explains that this "coincides with the physiological environment where chymosin is active--the calf stomache." Id. Thus, it appears that the reason the literature is replete with reference to pH of about 2 is because persons skilled in the art have attempted to optimize autocatalytic cleavage by simulating the physical environment within the calf stomache, which is at a pH of about 2. This optimum is consistent with the teaching of Ward and Foltman. Applicant agrees that Larson does not teach activation, but absorption--which are not the same. See Office Action, page 12 ("absorption and activation are non-analogous processes"). Therefore, nothing in Larson suggests that a pH of 2.0 is not an optimum pH for autocatalytic cleavage.

The Examiner views Larsen as teaching that chymosin can be activated at a pH as low as 0.5 and states that activation at a pH of 0.5 "is an art-recognized equivalent to activating chymosin at a pH of 2.0." However, Larson's teaching of a general range of pH between 0.5 and 5.0 would not convince the objective person of ordinary skill in the art that any of the pH values within this broad range would yield equivalent activation when the above teachings of Ward, Foltman, and Kühnel teach otherwise. Specifically, Kühnel teaches that a pH of about 2 is optimum, while Foltman teaches that the highest yield of chymosin was obtained at a pH of 2. Ward is consistent with Kühnel and Foltman in that it teaches using a pH of about 2. The weight of the evidence clearly suggests that a person of ordinary skill in the art would have though that a pH of 2.0 would be optimum for activation of chymosin. The Office Action fails to show a

single prior art teaching that is concerned with reducing glucoamylase activity or that specifically teaches that chymosin activation can be improved using a pH of less than 2. Accordingly, the weight of the evidence strongly suggests that persons having ordinary skill in the art would have activated chymosin at a pH of 2 thinking that that pH is the optimum pH for activation and would not have been motivated to utilize pH levels below 2.

For all the foregoing reasons, the Office Action fails to establish a prima facie case of obviousness of claims 5-6, 9, 12-14, 16-18, 29-31, and 42-43 under 35 U.S.C. § 103 based on Ward in view of Larsen.

"When evidence of secondary considerations such as unexpected results is initially before the Office, for example in the specification, that evidence should be considered in deciding whether there is a prima facie case of obviousness." M.P.E.P. § 2144.08. The Examiner focuses on the pH ranges in the claim without consideration of the claimed invention as a whole and evidence in the specification when discussing unexpected results. For instance, the Examiner seems to compare pH values of 2.0 with 1.99. Applicant notes that the present claims require a pH in the range of 1.0 to 1.8. Furthermore, without benefit of having read Applicant's disclosure, a person of ordinary skill in the art could not foresee the reduction of glucoamylase activity brought about by practicing the claimed process. Instead of expecting to reduce glucoamylase activity, a person of ordinary skill in the art (without having knowledge of the Applicant's disclosure) would only expect to reduce the chymosin activity by lowering the pH below 2.0 (not the glucoamylase activity). Thus, neither Ward nor Larsen, alone or in combination, teach or suggest the claimed process of "reducing the glucoamylase activity in a milk clotting composition." Claim 9 is thus unobvious in view of the combined teachings of Ward and Larsen. Claims 5-6, 9-14, 16-18, 29-31, 35-36, and 42-43 are likewise unobvious as they depend from and incorporate the limitations of claim 9. Applicant also submits that the dependent claims deserve separate patentability consideration because they introduce further limitations not found in either Ward or Larsen. Accordingly, the rejection of claims 5-6, 9-14, 16-18, 29-31, 35-36, and 42-43 under 35 U.S.C. § 103 must be withdrawn.

Applicant submits that this response addresses all of the issues raised in the Office Action and places the pending claims in condition for allowance. Should any issues remain to be discussed in this application, the undersigned may be reached by telephone. In the event any variance exists between the amount authorized to be charged to the Deposit Account and the Patent Office charges for reconsideration of this application, please charge or credit any difference to the undersigned's Deposit Account No. 50-0206.

Respectfully submitted,
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